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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,736	07/03/2003	Arthur M. Krieg	C1037.70044US00	4723

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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,736	KRIEG, ARTHUR M.	
	Examiner	Art Unit	
	NINA A. ARCHIE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,17-21,28-33 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-15 and 17-21,23,28-33,44,46-58,64-66,71-74,77-81,84,85,89,90,95,96,98 and 99.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 14,15,46-58,64-66,71-74,77-81,84,85,89,90,95,96,98 and 99.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :4/29/2004, 10/27/2004, 3/21/2005, 12/8/2006, 10/17/2007 .

DETAILED ACTION

1. The claims need to be renumbered to be in accordance with Rule 1.121.

Priority

2. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

3. The drawings in this application have been accepted. No further action by Applicant is required.

Specification

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Information Disclosure Statement

5. The information disclosure statements filed on 4/29/2004, 10/27/2004, 3/21/2005, 12/8/2006, 10/17/2007 has been considered. Initialed copies are enclosed.

Election/Restrictions

6. Applicant's election with traverse of Group I claims is acknowledged. The traversal is on the ground(s) that Applicant traverses the requirement to elect between a microbial antigen and a peptide antigen since these species are not mutually exclusive. Applicant intends by its election to embrace viral antigens that are peptide in nature. The traversal is also on the ground(s) that Applicant further traverses the requirement to elect between a local and a parenteral route of administration since these species are not mutually exclusive. Applicant intends by its election to embrace parenteral routes of administration that are also local routes of administration. Examiner withdraws the

election of species between microbial and peptide antigen and the election of species of routes of administration between locally and parental.

Claims 14-15, 46-58, 64-66, 71-74, 77-81, 84-85, 89, 90, 95-96, 98-99 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species or nonelected group (Group I claims 14-15), (Group II claims 46-58, 64-66, 71-74, 77-81, 84-85, 89, 90, 95-96, and 98), and (Group III claim 99), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on 11/19/2007.

Claim Objections

7. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). The claims need to be renumbered. Appropriate correction is advised.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-13, 17-21, 28-33, and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;
(B)The nature of the invention;
(C)The state of the prior art;
(D)The level of one of ordinary skill;
(E)The level of predictability in the art;
(F)The amount of direction provided by the inventor;
(G)The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Breadth of the claims: The claims are broadly drawn to a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1, further comprising any type of microbial/viral antigen and anti-microbial/anti-viral agent.

The nature of the invention: The claims are drawn to a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1.

The state of the prior art: In the instant, the involvement of a Thl type immune response in combating against intracellular pathogens is a well-recognized general concept. The art acknowledges the importance of Thl type immune response, which is stimulated by the production of Thl associated Cytokines, in the elimination of intracellular pathogens, including viruses. However, the art has not accredited or recognized any one particular Thl-associated cytokine to the amelioration of viral infection in a subject. Specifically, the art teaches that while cytokines secreted by T helper cells are of critical importance for the outcome of many infectious diseases, the production of the "right" set of cytokines can be a matter of life or death, as noted by Infante-Duarte et al. Infante-Duarte et al. further notes that in addition to a Thl type immune response, a Th2 type immune response is also necessary. Specifically, Infante-Duarte et al. teaches that a tight control over where and when Thl and Th2 immune responses happen is necessary to keep intracellular infections under control, and to prevent the Thl type immune response from causing damage to the host.1 Hence, while the importance of a Thl type immune response is well recognized in the art, the art further notes that a balance between Thl and Th2 type immune responses is necessary to resolve an infection. The cytokine art also provides that the efficacy of Thl associated cytokines, such as interleukin 2, interleukin 12 and interleukin 18, against intracellular pathogens are controversial, as evidenced by several references discussed below. Aoki et al. teaches that while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent M. bovis infection. Bohn et al. teaches that interleukin-12, a Thl associated cytokine, induces different effector mechanisms that result in either protection or exacerbation of a disease. Sakao et al. teaches that interleukin 18, a Thl associated cytokine, is responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18. Zaitseva et al. teaches that both interleukin 6 and interferon gamma augment the susceptibility of monocyte-derived macrophages to infection. Masihi, K. notes that interleukin 2 increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies.

In summation, the art teaches that cytokines can be inherently toxic, have unclear pharmacological behavior and also have pleiotropic effects. Hence, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated. (Infante-Duarte et al., Thl/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338). [Paragraph bridging pages 321-322, in particular.]; (Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236). [Lines 4-15, left column, page 229,in particular]; (Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains Infect. Immune., 1998, Vol. 66, 2213-2220) [Abstract, in particular.]; (Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11,471-480) [Abstract, in particular.]; (Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection) Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]; (Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin.Biol. Ther., 2001, Vol. 1, No. 4, 641-653) [Lines 15-25, left column of page 646, in particular].

Additionally, while the art teaches that oligonucleotides containing the CpG motif are capable of stimulating a Thl type immune response, however, the art also teaches that the Thl associated cytokine profile for these oligonucleotides vary from one oligonucleotide and species of subject to the next, as evidenced by Krieg et al. and Mutwiri et al. Krieg et al notes that each oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. Krieg et al. particularly notes that the type of cytokine stimulated by oligonucleotides containing the CpG motif is distinct from one oligonucleotide to the next. Additionally, both Krieg et al. and Mutwiri et al. note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif; ii) the spacings between CpG motifs; iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG

motif is presented in the sequence. The CpG art further teaches that Mutwiri et al. that Table 1 of Mutwiri et al. provides that the in vitro immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Furthermore, both Krieg et al. and Mutwiri et al. sets forth that the recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Thl associated cytokines. However, Mutwiri et al. provides that TLR-9 has only been identified in mice and humans. Mutwiri et al. also provides that the TLR-9 is differentially expressed in humans and mice. Hence, if the recognition of the CpG motif were dependent of TLR-9, then it would logically follows that the extent of the Thl type immune response induced by the oligonucleotide would necessarily vary from one species to the next. Mutwiri et al. also sets forth that in vitro observations do not accurately predict what happens in vivo (Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103). [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90.] (Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760). [paragraph that bridge pages 716-717, in particular.]

Predictability or unpredictability of the art:

As discussed above, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated. The art also recognizes that use of CpG to stimulate cytokine production, the use of the induced cytokine to influence viral infection, and the development of treatment regimen unpredictable and complicated. The art additionally teaches that the efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen have proven to be challenging and elusive.

Quantity of experimentation necessary:

Extreme undue burden of experimentation would be imposed upon the skilled artisan practicing the claimed invention. As stated above, Applicant has not provided much, if any, guidance or direction relating to the claimed invention. All that Applicant has provided is a conclusion that is made on the basis of generalized concepts that are well known in the art. And the formation of a conclusion based on generalized concepts renders the conclusion flawed. Generalized concepts are directed to support a general direction of studies or research; however, they do not support concrete conclusions. Concrete conclusions must be substantiated by facts, including evidence. In the instant, while the general direction of research may be outlined for the skilled artisan, the skilled artisan would not readily be able to practice the claimed invention without the undue burden of experimentation. Hence, in view of the lack of any guidance in the specification concerning the effective use of the claimed invention further comprising a microbial/viral antigen and a anti-microbial/anti-viral agent would not be able to reasonably practice the claimed invention without an undue burden experimentation.

The existence of working example:

The claims are directed to compositions comprising an immunostimulatory nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1 and a pharmaceutically acceptable carrier. The specification sets forth numerous in vitro and in vivo examples of using immunostimulatory nucleic acids; see for example, pgs. 87-95. The specification discloses that SEQ ID NO: 1 discloses the ability of the nucleic acid having a nucleic acid having a nucleotide sequence of SEQ ID NO:1 to protect murine subjects challenged with Herpes Simplex Virus 2 (see pg. 24). The specification discloses viruses that have been found in humans (see pg. 32-33). The specification discloses microbial antigens (see pgs. 32-33). The specification also discloses antiviral agents (see pg. 56). The specification also discloses various routes of administration. The specification does not set forth any examples with regard to using the claimed composition further comprising an microbial/viral antigen, anti-microbial agent, or anti-viral agent. The specification does not predict or teach any positive therapeutic benefit of the composition.

In conclusion, the claimed invention is not enabled for a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1. The claims are broadly drawn to a composition comprising an immunostimulatory nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1, further comprising any type of microbial/viral antigen and anti-microbial/anti-viral agent. The specification does not set forth any examples with regard to using the claimed composition further comprising an microbial/viral antigen, anti-microbial agent, or anti-viral agen. The specification does not predict or teach any positive therapeutic benefit of the composition. Hence, in view of the lack of any guidance in the specification concerning the effective use of the claimed invention further comprising a microbial/viral antigen and a anti-microbial/anti-viral agent would not be able to reasonably practice the claimed invention without an undue burden experimentation. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed product for the use as recited in the preamble.

Status of the Claims

9. No claims are allowed.

Claims 1-13, 17-21, 28-33, and 44 are rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie
Examiner
GAU 1645
REM 3B31

MARK NAVARRO
PRIMARY EXAMINER